

Non Technical Abstract

Central to the realization of the potential of gene therapy for cancer is the ability to accomplish efficient and specific gene delivery to cancer cells. In addition, the methods used to evaluate gene transfer are invasive and associated with bias. To this end, the Gene Therapy Program at UAB has developed a major focus in the area of gene therapy vector design and improvement. Specifically, we have shown that adenoviral vectors can be manufactured to target cancer cells and accomplish enhanced gene delivery when compared to unmodified adenoviral vectors. We have also genetically modified the vector to allow for non-invasive imaging of gene transfer using available radiologic methods. It is our hypothesis that modifications of adenoviral vectors to increase their specificity and efficiency will allow enhanced entry into tumor cells, and by virtue of this achievement, an enhanced therapeutic effect in the context of ovarian cancer. Accordingly, this research proposal includes a human gene therapy protocol for ovarian and extraovarian cancer patients with persistent or recurrent disease. This Phase I protocol will: 1) Determine the maximally tolerated dose of RGD genetically modified adenovirus encoding Herpes Simplex Virus thymidine kinase (HSV-TK) delivered into the abdominal cavity and given in combination with intravenous ganciclovir (GCV) in previously treated ovarian and extraovarian cancer patients. The spectrum of toxicities encountered with intraperitoneal delivery of this vector will be identified. 2) Determine the efficiency and specificity at which RGD genetically modified adenovirus accomplishes gene transfer to intraabdominal ovarian cancer cells when compared to normal cells. 3) Determine antibody response generated against the RGD modified adenovirus encoding HSV-TK when administered intraabdominally to patients with recurrent ovarian cancer. 4) Determine the ability to radiographically image adenoviral encoded human somatostatin receptor (hSSTr) after administration of a radiolabeled peptide (Tc-99m-P829) as a noninvasive method of evaluating gene transfer. This novel vector strategy has been highly promising in preclinical studies. It is anticipated that the experiments described would establish the safety and provide an indication of efficacy of this approach in human subjects with ovarian cancer and allow the rapid evaluation of the clinical utility of this novel therapeutic in future Phase II/III trials.